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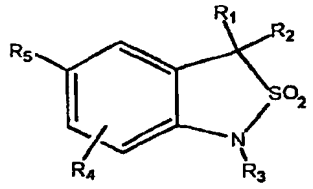

(1)

(57) Abstract

This invention relates to cyclic combination therapies utilizing, in combination with a progestin, an estrogen, or both, progesterone receptor antagonists of general structure (1): wherein the substituents are as defined herein; or pharmaceutically acceptable salt thereof.

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CONTRACEPTIVE COMPOSITIONS CONTAINING 2,1-BENZISOTHIAZOLINE 2,2-DIOXIDES AND PROGESTATIONALS

Background of the Invention

Intracellular receptors (IR) form a class of structurally related gene regulators known as "ligand dependent transcription factors" (R. M. Evans, *Science* **240**, 889, 1988). The steroid receptor family is a subset of the IR family, including progesterone receptor (PR), estrogen receptor (ER), androgen receptor (AR), glucocorticoid receptor (GR), and mineralocorticoid receptor (MR).

The natural hormone, or ligand, for the PR is the steroid progesterone, but synthetic compounds, such as medroxyprogesterone acetate or levonorgestrel, have been made which also serve as ligands. Once a ligand is present in the fluid surrounding a cell, it passes through the membrane *via* passive diffusion, and binds to the IR to create a receptor/ligand complex. This complex binds to specific gene promoters present in the cell's DNA. Once bound to the DNA the complex modulates the production of mRNA and protein encoded by that gene.

A compound that binds to an IR and mimics the action of the natural hormone is termed an agonist, whilst a compound that inhibits the effect of the hormone is an antagonist.

PR agonists (natural and synthetic) are known to play an important role in the health of women. PR agonists are used in birth control formulations, typically in the presence of an ER agonist. ER agonists are used to treat the symptoms of menopause, but have been associated with a proliferative effect on the uterus that can lead to an increased risk of uterine cancers. Co-administration of a PR agonist reduces or ablates that risk.

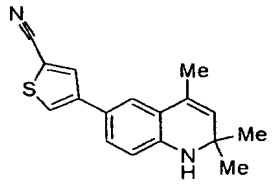
PR antagonists may also be used in contraception. In this context they may be administered alone (Ulmann *et al*, *Ann. N.Y. Acad. Sci.* **261**, 248, 1995), in combination with a PR agonist (Kekkonen *et al*, *Fertility and Sterility* **60**, 610, 1993) or in combination with a partial ER antagonist such as tamoxifen (WO 96/19997 A1 July 4, 1996).

PR antagonists may also be useful for the treatment of hormone dependent breast cancers (Horwitz *et al*, Horm. Cancer, 283, pub: Birkhaeuser, Boston, Mass., ed. Vedeckis) as well as uterine and ovarian cancers. PR antagonists may also be useful for the treatment of non-malignant chronic conditions such as fibroids (Murphy *et al, J. Clin. Endo. Metab.* **76**, 513, 1993) and endometriosis (Kettel *et al, Fertility and Sterility* **56**, 402, 1991).

PR antagonists may also be useful in hormone replacement therapy for post menopausal patients in combination with a partial ER antagonist such as tamoxifen (US 5719136).

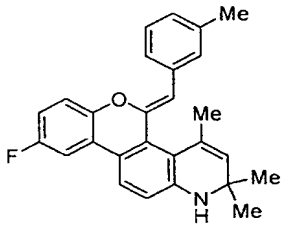
PR antagonists, such as mifepristone and onapristone, have been shown to be effective in a model of hormone dependent prostate cancer, which may indicate their utility in the treatment of this condition in men (Michna *et al*, *Ann. N.Y. Acad. Sci.* **761**, 224, 1995).

Jones *et al* (US 5,688,810) is the PR antagonist dihydroquinoline **A**.



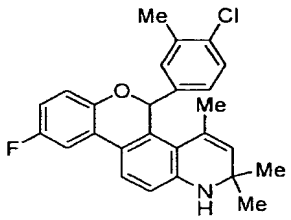
A

Jones *et al* described the enol ether **B** (US 5,693,646) as a PR ligand.



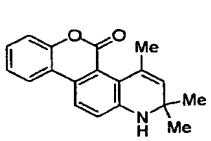
B

Jones *et al* described compound **C** (US 5,696,127) as a PR ligand.

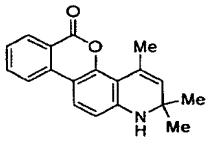


C

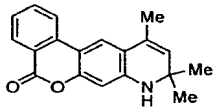
Zhi *et al* described lactones **D**, **E** and **F** as PR antagonists *(J. Med. Chem.* **41**, 291, 1998).



D

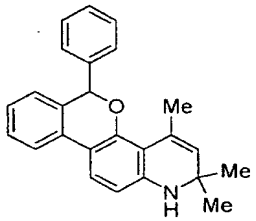


E



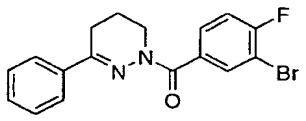
F

Zhi *et al* described the ether **G** as a PR antagonist *(J. Med. Chem.* **41**, 291, 1998).



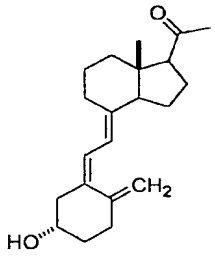
G

Combs *et al* disclosed the amide **H** as a ligand for the PR (*J. Med. Chem.* **38**, 4880, 1995).



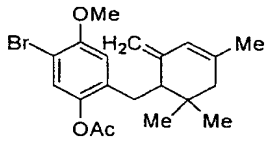
H

Perlman *et al* described the vitamin D analog **I** as a PR ligand (*Tetrahedron. Lett.* **35**, 2295, 1994).



I

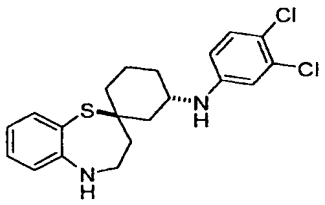
Hamann *et al* described the PR antagonist **J** (*Ann. N.Y. Acad. Sci.* **761**, 383, 1995).



J

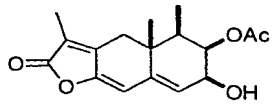
Chen *et al* described the PR antagonist **K** (Chen *et al*, POI-37, 16th Int. Cong. Het. Chem., Montana, 1997).

5



K

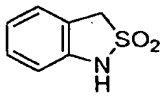
Kurihari *et al* described the PR ligand **L** (*J. Antibiotics* **50**, 360, 1997).



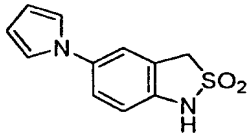
L

There are several examples of 2,1-benzisothiazoline 2,2-dioxides ('sultams') in the chemical and patent literature which contain no reference to progesterone activity, and do not carry the correct substitution pattern for PR modulator activity.

Chiarino *et al* described the preparation of the parent 2,1-benzisothiazoline 2,2-dioxide, i.e., **M** (and derivatives, e.g., **N**), that was used in the present invention *(J. Heterocycl. Chem.* **23(6),** 1645-9, 1986).

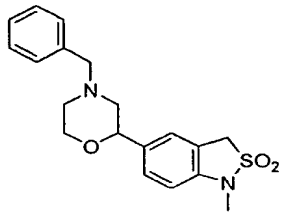


M



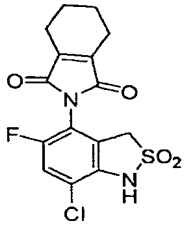
N

Skorcz *et al* described a series of 5-(2-morpholinyl)-2,1-benzisothiazolines, e.g., **O**, which are useful as central nervous depressants (U.S. 3,635,964).

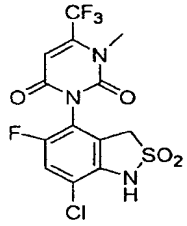


O

Kamireddy *et al* disclosed a series of cyclic sulfonamides, e.g., **P** and **Q**, useful for controlling undesired vegetation (WO 95/33746).



P



Q

Description of the Invention

This invention provides combination therapies and dosing regimens utilizing antiprogestational agents in combination with one or more progestational agents. This invention further provides methods of treatment and dosing regimens further utilizing in combination with these antiprogestins and progestins, an estrogen, such as ethinyl estradiol.

These regimens and combinations may be administered to a mammal to induce contraception or for the treatment and/or prevention of secondary amenorrhea, dysfunctional bleeding, uterine leiomyomata, endometriosis; polycystic ovary syndrome, carcinomas and adenocarcinomas of the endometrium, ovary, breast, colon, prostate. Additional uses of the invention include stimulation of food intake. The uses herein for the treatment and/or prevention of the conditions or diseases

described above includes the continuous administration or periodic discontinuation of administration of the invention to allow for minimization of effect dose or minimization of side effects or cyclic menstrual bleeding.

The use of this invention for contraception includes administration, preferably orally, to a female of child bearing age an antiprogestin in combination with an estrogen or progestin or both. These administration regimens are preferably carried out over 28 consecutive days, with a terminal portion of the cycle containing administration of no progestins, estrogens or anti-progestins.

The progestins of these combinations may be administered alone or in combination with an estrogen for the first 14 to 24 days of the cycle, the progestins being administered at a dosage range equal in progestational activity to about 35 μg to about 150 μg levonorgestrel per day, preferably equal in activity to from about 35 μg to about 100 μg levonorgestrel per day. An antiprogestin may then be administered alone or in combination with an estrogen for a period of 1 to 11 days to begin on any cycle day between day 14 and 24. The anti-progestin in these combinations may be administered at a dose of from about 2μg to about 50 μg per day and the estrogen may be administered at a dose of from about 10 μg to about 35 μg per day. In an oral administration, a package or kit containing 28 tablets will include a placebo tablet on those days when the antiprogestin or progestin or estrogen is not administered.

In a preferred embodiment of this invention, the progestins of this invention may be administered alone or in combination with estrogen for the initial 18 to 21 days of a 28-day cycle, followed by administration of an antiprogestin, alone or in combination with an estrogen, for from 1 to 7 days.

The estrogen to be used in the combinations and formulations of this invention is preferably ethinyl estradiol.

Progestational agents useful with this invention include, but are not limited to, levonorgestrel, norgestrel, desogestrel, 3-ketodesogestrel, norethindrone, gestodene, norethindrone acetate, norgestimate, osaterone, cyproterone acetate, trimegestone, dienogest, drospirenone, nomegestrol, or (17-deacetyl)norgestimate. Among the

preferred progestins for use in the combinations of this invention are levonorgestrel, gestodene and trimegestone.

Examples of orally administered regimens of this invention over a 28 day cycle include administration of a progestational agent solely for the first 21 days at a daily dose equal in progestational activity to from about 35 to about 100 μg of levonorgestrel. An antiprogestin compound of this invention may then be administered at a daily dose of from about 2 to 50 mg from day 22 to day 24, followed by no administration or administration of a placebo for days 25 to 28. It is most preferred that the daily dosages of each relevant active ingredient be incorporated into a combined, single daily dosage unit, totaling 28 daily units per 28-day cycle.

In another regimen, a progestational agent may be coadministered for the first 21 days at a daily dose equal in progestational activity to from about 35 to about 150 μg levonorgestrel, preferably equal in activity to from about 35 to about 100 μg levonorgestrel, with an estrogen, such as ethinyl estradiol, at a daily dose range of from about 10 to about 35 μg. This may be followed as described above with an antiprogestin administered at a daily dose of from about 2 to 50 mg from day 22 to day 24, followed by no administration or administration of a placebo for days 25 to 28.

Still another regimen within the scope of this invention will include coadministration from days 1 to 21 of a progestational agent, the progestational agent, preferably levonorgestrel, being administered at a daily dose equal in progestational activity to from about 35 to about 100 μg levonorgestrel, and an estrogen, such as ethinyl estradiol, at a daily dose range of from about 10 to about 35 μg. This will be followed on days 22 to 24 by coadministration of an antiprogestin (2 to 50 mg/day) and an estrogen, such as ethinyl estradiol, at a daily dose of from about 10 to about 35 μg. From day 25 to day 28, this regimen may be followed by no administration or administration of a placebo.

This invention also kits or packages of pharmaceutical formulations designed for use in the regimens described herein. These kits are preferably designed for daily

oral administration over a 28-day cycle, preferably for one oral administration per day, and organized so as to indicate a single oral formulation or combination of oral formulations to be taken on each day of the 28-day cycle. Preferably each kit will include oral tablets to be taken on each the days specified, preferably one oral tablet will contain each of the combined daily dosages indicated.

According to the regimens described above, one 28-day kit may comprise:

a) an initial phase of from 14 to 21 daily dosage units of a progestational agent equal in progestational activity to about 35 to about 150 μg levonorgestrel, preferably equal in progestational activity to about 35 to about 100 μg levonorgestrel;

b) a second phase of from 1 to 11 daily dosage units of an antiprogestin compound of this invention, each daily dosage unit containing an antiprogestin compound at a daily dosage of from about 2 to 50 mg; and

c) optionally, a third phase of an orally and pharmaceutically acceptable placebo for the remaining days of the cycle in which no antiprogestin, progestin or estrogen is administered.

A preferred embodiment of this kit may comprise:

a) an initial phase of 21 daily dosage units of a progestational agent equal in progestational activity to about 35 to about 150 μg levonorgestrel, preferably equal in progestational activity to about 35 to about 100 μg levonorgestrel;

b) a second phase of 3 daily dosage units for days 22 to 24 of an antiprogestin compound of this invention, each daily dosage unit containing an antiprogestin compound at a daily dosage of from about 2 to 50 mg; and

c) optionally, a third phase of 4 daily units of an orally and pharmaceutically acceptable placebo for each of days 25 to 28.

Another 28-day cycle packaging regimen or kit of this invention comprises:

a) a first phase of from 18 to 21 daily dosage units of a progestational agent equal in progestational activity to about 35 to about 150 μg levonorgestrel, preferably equal in activity to from about 35 to about 100 μg levonorgestrel, and, as

an estrogen, ethinyl estradiol at a daily dose range of from about 10 to about 35 μg; and

b) a second phase of from 1 to 7 daily dosage units of an antiprogestin of this invention at a daily dose of from about 2 to 50 mg; and

c) optionally, an orally and pharmaceutically acceptable placebo for each of the remaining 0 to 9 days in the 28-day cycle in which no progestational agent, estrogen or antiprogestin is administered.

A preferred embodiment of the kit described above may comprise:

a) a first phase of 21 daily dosage units of a progestational agent equal in progestational activity to about 35 to about 150 μg levonorgestrel, preferably equal in activity to from about 35 to about 100 μg levonorgestrel, and, as an estrogen, ethinyl estradiol at a daily dose range of from about 10 to about 35 μg; and

b) a second phase of 3 daily dosage units for days 22 to 24 of an antiprogestin administered at a daily dose of from about 2 to 50 mg; and

c) optionally, a third phase of 4 daily dose units of an orally and pharmaceutically acceptable placebo for each of days 25 to 28.

A further 28-day packaged regimen or kit of this invention comprises:

a) a first phase of from 18 to 21 daily dosage units, each containing a progestational agent of this invention at a daily dose equal in progestational activity to about 35 to about 150 μg levonorgestrel, preferably equal in activity to from about 35 to about 100 μg levonorgestrel, and ethinyl estradiol at a daily dose range of from about 10 to about 35 μg;

b) a second phase of from 1 to 7 daily dose units, each daily dose unit containing an antiprogestin of this invention at a concentration of from 2 to 50 mg; and ethinyl estradiol at a concentration of from about 10 to about 35 μg; and

c) optionally, an orally and pharmaceutically acceptable placebo for each of the remaining 0 to 9 days in the 28-day cycle in which no progestational agent, estrogen or antiprogestin is administered.

A preferred embodiment of the package or kit just described comprises:

a) a first phase of 21 daily dosage units, each containing a progestational agent of this invention at a daily dose equal in progestational activity to about 35 to about 150 μg levonorgestrel, preferably from about 35 to about 100 μg levonorgestrel, and ethinyl estradiol at a daily dose range of from about 10 to about 35 μg;

b) a second phase of 3 daily dose units for days 22 to 24, each dose unit containing an antiprogestin of this invention at a concentration of from 2 to 50 mg; and ethinyl estradiol at a concentration of from about 10 to about 35 μg; and

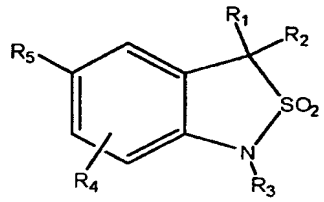
c) optionally, a third phase of 4 daily units of an orally and pharmaceutically acceptable placebo for each of days 25 to 28.

In each of the regimens and kits just described, it is preferred that the daily dosage of each pharmaceutically active component of the regimen remain fixed in each particular phase in which it is administered. It is also understood that the daily dose units described are to be administered in the order described, with the first phase followed in order by the second and third phases. To help facilitate compliance with each regimen, it is also preferred that the kits contain the placebo described for the final days of the cycle. It is further preferred that each package or kit comprise a pharmaceutically acceptable package having indicators for each day of the 28-day cycle, such as a labeled blister package or dial dispenser packages known in the art.

In this disclosure, the terms anti-progestational agents, anti-progestins and progesterone receptor antagonists are understood to be synonymous. Similarly, progestins, progestational agents and progesterone receptor agonists are understood to refer to compounds of the same activity.

These dosage regimens may be adjusted to provide the optimal therapeutic response. For example, several divided doses of each component may be administered daily or the dose may be proportionally increased or reduced as indicated by the exigencies of the therapeutic situation. In the descriptions herein, reference to a daily dosage unit may also include divided units that are administered over the course of each day of the cycle contemplated.

Antiprogestin compounds which may be used in the kits, methods and regimens herein are those of the Formula 1:



1

wherein

R_1 and R_2 are each, independently, hydrogen, alky, substituted alkyl, hydroxy, alkoxy, substituted alkoxy, aryl, substituted aryl, heteroaryl, substituted heteroary, arylalkyl, heteroarylalkyl, and alkynyl; or

R_1 and R_2 are taken together form a ring and together contain $-CH_2(CH_2)_nCH_2-$, $-CH_2CH_2CMe_2CH_2CH_2-$, $-O(CH_2)_pCH_2-$, $O(CH_2)_qO-$, $-CH_2CH_2OCH_2CH_2-$, $-CH_2CH_2NR_7CH_2CH_2-$; or

R_1 and R_2 are a double bond, said double bond having two methyl groups bonded to the terminal end, having a cycloalkyl group bonded to the terminal end, having an oxygen bonded to the terminal end, or having a cycloether bonded to the terminal end;

R_7 is hydrogen or alkyl of 1-6 carbon atoms;

n = 1-5;

p = 1-4;

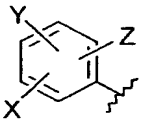
q = 1-4;

R^3 is hydrogen, hydroxyl, NH_2, alkyl, substituted alkyl, alkenyl, alkynyl, substituted or, COR^A;

R^A is hydrogen, alkyl, substituted alkyl, alkoxy, substituted alkoxy, aminoalkyl, or substituted aminoalkyl;

R^4 is hydrogen, halogen, -CN, $-NH_2$, alkyl, substituted alkyl, alkoxy, alkoxy, aminoalkyl, or substituted aminoalkyl;

R^5 is a trisubstituted phenyl ring having the structure,



;

X is halogen, OH, -CN, alkyl, substituted alkyl, alkoxy, substituted alkoxy, thioalkyl, substituted thioalkyl, S(O)alkyl, $S(O)_2$alkyl, aminoalkyl, substituted aminoalkyl, $-NO_2$, perfluoroalkyl, 5 or 6 membered heterocyclic ring containing 1 to 3 heteroatoms, thioalkoxy, $-COR^B$, $-OCOR^B$, or $-NR^CCOR^B$;

R^B is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, alkoxy, substituted alkoxy, aminoalkyl, or substituted aminoalkyl;

R^C is hydrogen, alkyl, or substituted alkyl;

Y and Z are each, independently, hydrogen, halogen, -CN, $-NO_2$, alkoxy, alkyl, or thioalkyl; or

R^5 is a five or six membered heteroaryl ring containing 1, 2, or 3 heteroatoms selected from the group consisting of O, S, SO, SO_2 and NR^6 with said ring carbons being optionally substituted with one or two substituents independently selected from the group consisting of hydrogen, halogen, CN, NO_2 alkyl, alkoxy, aminoalkyl, COR^D, and NR^ECOR^D;

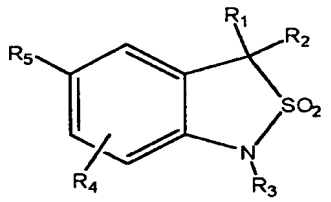
R^D is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, alkoxy, substituted alkoxy, aminoalkyl, or substituted aminoalkyl;

R^E is hydrogen, alkyl, or substituted alkyl;

R^6 is hydrogen, alkyl, alkoxycarbonyl, or is absent when the nitrogen of NR^6 is bonded to a ring double bond;

or pharmaceutically acceptable salt thereof.

Preferred antiprogestin compounds for use with the methods and regimens this invention are those having the structure:



1

wherein

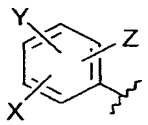
R_1 and R_2 are taken together form a ring and together contain $-CH_2(CH_2)_nCH_2-$;

n = 2-3;

R^3 is hydrogen;

R^4 is hydrogen;

R^5 is a trisubstituted phenyl ring having the structure,



;

X is halogen, OH, -CN, alkyl, alkoxy, thioalkyl, substituted thioalkyl, S(O)alkyl, $S(O)_2$alkyl, aminoalkyl, substituted aminoalkyl, $-NO_2$, perfluoroalkyl, 5 or 6 membered heterocyclic ring containing 1 to 3 heteroatoms, or thioalkoxy;

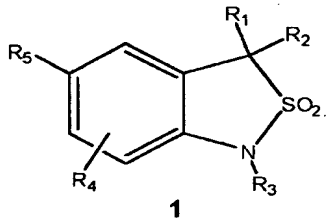
Y and Z are each, independently, hydrogen, halogen, -CN, $-NO_2$, alkoxy, alkyl, or thioalkyl; or

R^5 is a five or six membered heteroaryl ring containing 1, 2, or 3 heteroatoms selected from the group consisting of O, S, and NR^6 with said ring carbons being optionally substituted with one or two substituents independently selected from the group consisting of hydrogen, halogen, CN, NO_2 , alkyl, or alkoxy;

R^6 is hydrogen, alkyl, alkoxycarbonyl, or is absent when the nitrogen of NR^6 is bonded to a ring double bond;

or pharmaceutically acceptable salt thereof.

More preferred compounds of this invention are those having the structure



1

wherein

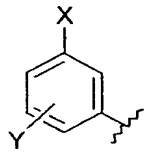
R_1 and R_2 are taken together form a ring and together contain $-CH_2(CH_2)_nCH_2-$;

n = 2-3;

R^3 is hydrogen;

R^4 is hydrogen;

R^5 is a disubstituted phenyl ring having the structure,



;

X is halogen, -CN, or $-NO_2$;

Y is hydrogen, halogen, -CN, $-NO_2$, alkoxy, alkyl, or thioalkyl; or

R^5 is a five or six membered heteroaryl ring containing a heteroatom selected from the group consisting of O, S, and NR^6 with said ring carbons being optionally substituted with one or two substituents independently selected from the group consisting of hydrogen, halogen, CN, or NO_2 ;

R^6 is hydrogen, or is absent when the nitrogen of NR^6 is bonded to a ring double bond;

or pharmaceutically acceptable salt thereof.

The antiprogestin compounds of this invention may contain an asymmetric carbon atom and some of the compounds of this invention may contain one or more asymmetric centers and may thus give rise to optical isomers and diastereoisomers. While shown without respect to stereochemistry in Formula **1**, the present invention includes such optical isomers and diastereoisomers; as well as the racemic and resolved, enantiomerically pure R and S stereoisomers; as well as other mixtures of the R and S stereoisomers and pharmaceutically acceptable salts thereof.

The term "alkyl" is used herein to refer to both straight- and branched-chain saturated aliphatic hydrocarbon groups having 1 to 6 carbon atoms; "alkenyl" includes both straight- and branched-chain alkyl group of 2 to 6 carbon atoms containing at least one carbon-carbon double bond; "alkynyl" group includes both straight- and branched-chain alkyl group of 2 to 6 carbon atoms with at least one carbon-carbon triple bond.

The terms "substituted alkyl", "substituted alkenyl", and "substituted alkynyl" refer to alkyl, alkenyl, and alkynyl as containing one or more substituents from the group including halogen, CN, OH, NO_2, amino, aryl, heterocyclic, substituted aryl, substituted heterocyclic, alkoxy, aryloxy, substituted alkyloxy, alkylcarbonyl, alkylcarboxy, alkylamino, arylthio. These substituents may be attached to any carbon of alkyl, alkenyl, or alkynyl group provided that the attachment constitutes a stable chemical moiety.

The term "aryl" is used herein to refer to an aromatic system of 6 to 14 carbon atoms, which may be a single ring or multiple aromatic rings fused or linked together as such that at least one part of the fused or linked rings forms the conjugated aromatic system. Preferred aryl groups include phenyl, naphthyl, biphenyl, anthryl, tetrohydronaphthyl, phenanthryl groups.

The term "substituted aryl" refers to aryl substituted by one or more substituents from the group including halogen, CN, OH, NO_2, amino, alkyl, cycloalkyl, alkenyl, alkynyl, alkoxy, aryloxy, substituted alkyloxy, alkylcarbonyl, alkylcarboxy, alkylamino, or arylthio.

The term "heterocyclic" is used herein to describe a stable 4 to 14 membered monocyclic or multicyclic heterocyclic ring which is saturated, partially unsaturated, or unsaturated, and which consists of carbon atoms and from one to four heteroatoms selected from the group including N, O, and S atoms. The N and S atoms may be oxidized, as an N-oxide, sulfoxide, or sulfone. The heterocyclic ring also includes any multicyclic ring in which any of above defined heterocyclic rings is fused to an aryl ring. The heterocyclic ring may be attached at any heteroatom or carbon atom provided the resultant structure is chemically stable. Such heterocyclic groups include, for example, tetrahydrofuran, piperidinyl, piperazinyl, 2-oxopiperidinyl, azepinyl, pyrrolidinyl, imidazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, isoxazolyl, morpholinyl, indolyl, quinolinyl, thienyl, furyl, benzofuranyl, benzothienyl, thiamorpholinyl, thiamorpholinyl sulfoxide, and isoquinolinyl.

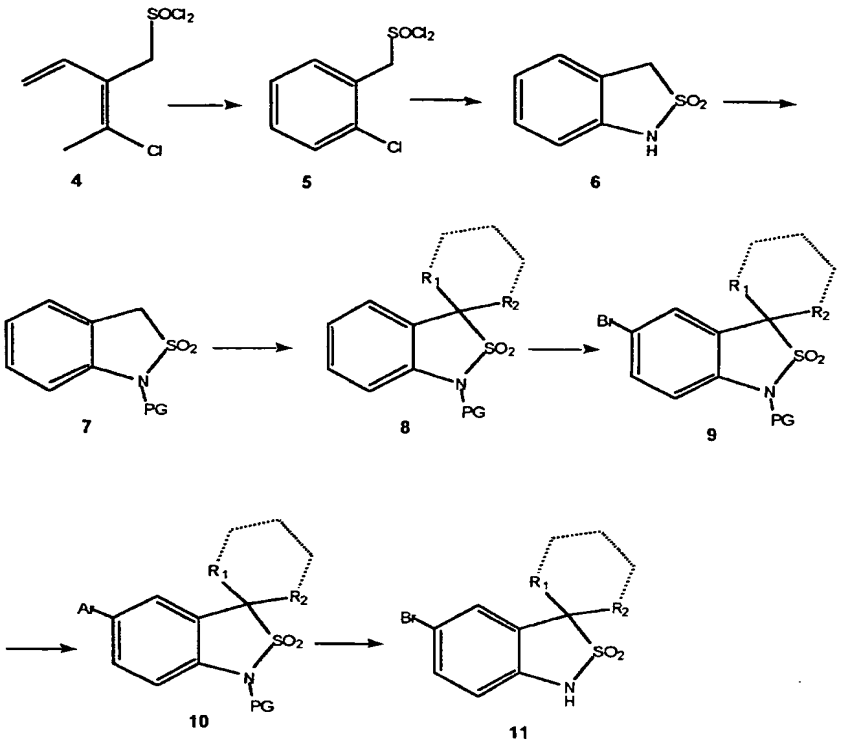
The term "substituted heterocyclic" is used herein to describe a heterocyclic having one or more substituents selected from the group which includes halogen, CN, OH, NO_2, amino, alkyl, substituted alkyl, cycloalkyl, alkenyl, substituted alkenyl, alkynyl, alkoxy, aryloxy, substituted alkyloxy, alkylcarbonyl, alkylcarboxy, alkylamino, or arylthio. The term "thioalkyl" is used herein to refer to the SR group, where R is alkyl or substituted alkyl. The term "alkoxy" is used herein to refer to the OR group, where R is alkyl or substituted alkyl. The term "aryloxy" is used herein to refer to the OR group, where R is aryl or substituted aryl. The term "alkylcarbonyl" is used herein to refer to the RCO group, where R is alkyl or substituted alkyl. The term "alkylcarboxy" is used herein to refer to the COOR group, where R is alkyl or substituted alkyl. This term is also referred to as alkoxycarbonyl. The term "aminoalkyl" refers to both secondary and tertiary amines wherein the alkyl or substituted alkyl groups may be either same or different and the point of attachment is on the nitrogen atom. The term "halogen"is defined as Cl, Br, F, and I.

Pharmaceutically acceptable salts can be formed of these antiprogestin compounds from organic and inorganic acids, for example, acetic, propionic, lactic, citric, tartaric, succinic, fumaric, maleic, malonic, mandelic, malic, phthalic, hydrochloric, hydrobromic, phosphoric, nitric, sulfuric, methanesulfonic,

napthalenesulfonic, benzenesulfonic, toluenesulfonic, camphorsulfonic, and similarly known acceptable acids. Salts may also be formed from inorganic bases, preferably alkali metal salts, for example, sodium, lithium, or potassium, and organic bases, such as ammonium, mono-, di-, and trimethylammonium, mono-, di- and triethylammonium, mono-, di- and tripropylammonium (iso and normal), ethyl-dimethylammonium, benzyldimethylammonium, cyclohexylammonium, benzyl-ammonium, dibenzylammonium, piperidinium, morpholinium, pyrrolidinium, piperazinium, 1-methylpiperidinium, 4-ethylmorpholinium, 1-isopropylpyrrolidinium, 1,4-dimethylpiperazinium, 1-n-butyl piperidinium, 2-methylpiperidinium, 1-ethyl-2-methylpiperidinium, mono-, di- and triethanolammonium, ethyl diethanolammonium, n-butylmonoethanolammonium, tris(hydroxymethyl)methylammonium, phenylmono-ethanolammonium, and the like.

The antiprogestin compounds of this invention were be prepared according to the following schemes from commercially available starting materials or starting materials which can be prepared using literature procedures. These schemes show the preparation of representative antiprogestin compounds of this invention.

Scheme 1



According to Scheme 1, commercially available sulfonyl chloride **4** is converted *via* the sulfonamide **5** to the 2,1-benzisothiazoline 2,2-dioxide **6** as described in the literature (Chiarino *et al, J. Heterocycl. Chem.* **23(6),** 1645-9, 1986). The nitrogen atom of sultam **6** is then protected by a suitable protecting group, e.g., trimethyl silyl ethyl.

The protected sultam 7 next is treated with a strong organo-metallic base (e.g., butyl lithium, lithium diisopropylamide, potassium hexamethyldisilylazide) in an inert solvent (e.g., THF, diethyl ether) under nitrogen at reduced temperature (ca. -20°C) (Kende *et al*, *Synth. Commun.* **12**, 1, 1982). The resulting di-anion then is treated with

excess electrophile such as an alkyl halide, preferably the iodide. If R_1 and R_2 are to be joined such as the product contains a spirocycle at position 3, then the electrophile should be bifunctional, i.e., a diiodide. Subsequent bromination of the sultam **8** proceeds regioselectively at room temperature with bromine in acetic acid (an organic co-solvent such as dichloromethane may be added as required) in the presence of sodium acetate, to give the aryl bromide **9**. Judicious choice of reaction conditions may facilitate simultaneous removal of the protecting group at this step.

The bromide **9** then is reacted with a palladium salt (e.g., tetrakis(triphenylphoshine)palladium(0)), in a suitable solvent (e.g., THF, dimethoxyethane, ethanol, toluene) under an inert atmosphere (argon, nitrogen). The mixture then is treated with an arylboronic acid or arylboronic acid ester and a base (sodium carbonate, triethylamine, potassium phosphate) in water or fluoride source (cesium fluoride) under anhydrous conditions at elevated temperature to give the biphenyl sultam **10**. Finally, the protecting group is removed under appropriate conditions and the final product **11** is isolated and purified by standard means.

If R_1 and R_2 are different then the intermediate is prepared by reacting the dianion of **7** with one equivalent of the electrophile R_1-X (X = leaving group, e.g., iodide). The resultant mono-alkylated compound may be then isolated and re-subjected to the reaction conditions using R_2-X, or alternatively used *in situ* for the second alkylation with R_2-X. Alternatively, if the desired product is to contain R_2 = H, then the isolated mono-alkylated intermediate is taken though the subsequent steps.

9 **10**

Scheme 2

Other methodologies also are available for coupling the aryl group, Ar, to the sultam platform: for example, reaction of the bromide **9** with an aryl stannane, aryl zinc, or aryl magnesium halide in the presence of a palladium or nickel catalyst

(Scheme 2). The required aryl-metallic species are formed *via* standard techniques. Furthermore, the bromide **9** may be converted to an aryl boronic acid *via* standard procedures (treatment with n-butyllithium followed by addition of trimethyl borate and subsequent boronic ester hydrolysis) that will then undergo the range of previously described coupling procedures with a suitable aryl bromide.

The antiprogestational activity of the compounds of this invention was demonstrated in an in vitro standard pharmacological test procedure which evaluated the antiprogestational potency of a representative compound of this invention by measuring its effect on PRE-luciferase reporter activity in CV-1 cells co-transfected with human PR and PRE-luciferase plasmids. When evaluated in the above-described test procedure, the compound of Example 1 had an IC_{50} of 900 nM. The IC_{50} is the concentration of test compound that gives half-maximal decrease in 3 nM progesterone induced PRE-luciferase activity.

The results obtained in this standard pharmacological test procedure demonstrate that the compounds of this invention are progestational antagonists, and are therefore useful as oral contraceptives (male and female), in hormone replacement therapy (particularly when combined with an estrogen), in the treatment of endometriosis, luteal phase defects, benign breast and prostatic diseases and prostatic, breast, ovarian, uterine and endometrial cancers.

The antiprogestin compounds of this invention can be used alone as a sole therapeutic agent or can be used in combination with other agents, such as other estrogens, progestins, or androgens.

The antiprogestational compounds of this invention can be formulated neat or with a pharmaceutical carrier for administration, the proportion of which is determined by the solubility and chemical nature of the compound, chosen route of administration and standard pharmacological practice. The pharmaceutical carrier may be solid or liquid.

A solid carrier can include one or more substances which may also act as flavoring agents, lubricants, solubilizers, suspending agents, fillers, glidants, compression aids, binders or tablet-disintegrating agents; it can also be an encapsulating material. In powders, the carrier is a finely divided solid that is in admixture with the finely divided active ingredient. In tablets, the active ingredient is mixed with a carrier having the necessary compression properties in suitable proportions and compacted in the shape and size desired. The powders and tablets

preferably contain up to 99% of the active ingredient. Suitable solid carriers include, for example, calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl cellulose, polyvinylpyrrolidine, low melting waxes and ion exchange resins.

Liquid carriers are used in preparing solutions, suspensions, emulsions, syrups, elixirs and pressurized compositions. The active ingredient can be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent, a mixture of both or pharmaceutically acceptable oils or fats. The liquid carrier can contain other suitable pharmaceutical additives such as solubilizers, emulsifiers, buffers, preservatives, sweeteners, flavoring agents, suspending agents, thickening agents, colors, viscosity regulators, stabilizers or osmo-regulators. Suitable examples of liquid carriers for oral and parenteral administration include water (partially containing additives as above, e.g. cellulose derivatives, preferably sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols, e.g. glycols) and their derivatives, lethicins, and oils (e.g. fractionated coconut oil and arachis oil). For parenteral administration, the carrier can also be an oily ester such as ethyl oleate and isopropyl myristate. Sterile liquid carriers are useful in sterile liquid form compositions for parenteral administration. The liquid carrier for pressurized compositions can be halogenated hydrocarbon or other pharmaceutically acceptable propellant.

Liquid pharmaceutical compositions that are sterile solutions or suspensions can be utilized by, for example, intramuscular, intraperitoneal or subcutaneous injection. Sterile solutions can also be administered intravenously. The compounds of this invention can also be administered orally either in liquid or solid composition form.

The compounds of this invention may be administered rectally or vaginally in the form of a conventional suppository. For administration by intranasal or intrabronchial inhalation or insufflation, the compounds of this invention may be formulated into an aqueous or partially aqueous solution, which can then be utilized in the form of an aerosol. The compounds of this invention may also be administered transdermally through the use of a transdermal patch containing the active compound and a carrier that is inert to the active compound, is non toxic to the skin, and allows delivery of the agent for systemic absorption into the blood stream via the skin. The carrier may take any number of forms such as creams and ointments, pastes, gels, and

occlusive devices. The creams and ointments may be viscous liquid or semisolid emulsions of either the oil-in-water or water-in-oil type. Pastes comprised of absorptive powders dispersed in petroleum or hydrophilic petroleum containing the active ingredient may also be suitable. A variety of occlusive devices may be used to release the active ingredient into the blood stream such as a semipermeable membrane covering a reservoir containing the active ingredient with or without a carrier, or a matrix containing the active ingredient. Other occlusive devices are known in the literature.

The dosage requirements vary with the particular compositions employed, the route of administration, the severity of the symptoms presented and the particular subject being treated. Based on the results obtained in the standard pharmacological test procedures, projected daily dosages of active compound would be 0.02 μg/kg - 750 μg/kg. Treatment will generally be initiated with small dosages less than the optimum dose of the compound. Thereafter the dosage is increased until the optimum effect under the circumstances is reached; precise dosages for oral, parenteral, nasal, or intrabronchial administration will be determined by the administering physician based on experience with the individual subject treated. Preferably, the pharmaceutical composition is in unit dosage form, e.g. as tablets or capsules. In such form, the composition is sub-divided in unit dose containing appropriate quantities of the active ingredient; the unit dosage forms can be packaged compositions, for example, packaged powders, vials, ampoules, pre filled syringes or sachets containing liquids. The unit dosage form can be, for example, a capsule or tablet itself, or it can be the appropriate number of any such compositions in package form.

The following provides the preparation of a representative compound of this invention.

Example 1

5-(3-chlorophenyl)spiro[2,1-benzisothiazole-3(1H),1'-cyclohexane] 2,2-dioxide

To 1,3-dihydro-2,1-benzisothiazoline 2,2-dioxide (Chiarino *et al*, *J. Heterocycl. Chem.* **23(6),** 1645-9, 1986) (0.74 g, 4.4 mmol) in anhydrous dichloromethane (minimum amount) at room temperature was added sequentially N,N-diisopropylethylamine (0.76 mL, 4.4 mmol) and 2-(trimethylsilyl)ethoxymethyl chloride (0.77 mL, 4.4 mmol). After 30 min, the reaction was poured into water (50

mL), the layers were separated, and the aqueous phase was extracted with ethyl acetate (2 x 50 mL). The organic layers were combined, washed with brine (30 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo* to give *1,3-dihydro-1-(2'-trimethylsilylethyl)-2,1-benzisothiazoline 2,2-dioxide* (1.3 g, 99%) as an off-white solid. ^{1}H NMR ($CDCl_3$, 300MHz) δ 0.02 (s, 9 H), 0.97 (dd, 2 H, J = 8.3, 8.2 Hz), 3.73 (dd, 2 H, J = 8.2, 8.3 Hz), 4.40 (s, 2 H), 5.08 (s, 2 H), 7.05 (d, 1 H, J = 7.4 Hz), 7.07 (dd, 1 H), 7.26 (d, 1 H, J = 7.4 Hz), 7.35 ('t', 1 H, J = 7.6, 7.6 Hz). MS ((+) APCI *m/z* 317 $[M+NH_4]^+$.

To 1,3-dihydro-1-(2'-trimethylsilylethyl)-2,1-benzisothiazoline 2,2-dioxide (1.3 g, 4.3 mmol) in anhydrous tetrahydrofuran (13 mL) at room temperature was added 1,5-diiodopentane (1.29 mL, 8.6 mmol). The mixture was cooled to -78 °C and lithium bis(trimethylsilyl)amide (1.0 *M* solution in tetrahydrofuran, 17.3 mL, 17 mmol) was added. After 15 min, the reaction mixture was poured into water (50 mL), the layers were separated, and the aqueous phase was extracted with ethyl acetate (3 x 50 mL). The organic layers were combined, washed with brine (30 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. Purification by flash column chromatography (5% ethyl acetate/hexane) on silica gel gave *1,3-dihydro-3-spirocyclohexyl-1-(2'-trimethylsilylethyl)-2,1-benzisothiazoline 2,2-dioxide* (0.8 g, 51%) as an off-white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.00 (s, 9 H), 0.95 (dd, 2 H, J = 8.3, 8.2 Hz), 1.18-2.36 (m, 10 H), 3.72 (dd, 2 H, J = 8.2, 8.3 Hz), 5.06 (s, 2 H), 7.03 ('t', 1 H, J = 7.8 Hz), 7.06 (dd, 1 H, J = 1, 7.6 Hz), 7.18 (dd, 1 H, J = 1.1, 7.6 Hz), 7.28 (dt, 1 H, J = 1.3, 7.7 Hz). MS (EI) *m/z* 367 $[M]^+$.

To a stirred solution of 1,3-dihydro-3-spirocyclohexyl-1-(2'-trimethylsilylethyl)-2,1-benzisothiazoline 2,2-dioxide (0.8 g, 2.2 mmol) in glacial acetic acid (5 mL) at room temperature was added dropwise a solution of bromine (0.11 mL, 2.2 mmol) in glacial acetic acid (2.2 mL) After stirring for 10 min, anhydrous sodium acetate (0.18 g, 2.2 mmol) was added and the solution was concentrated *in vacuo*. The residue was dissolved in ethyl ether (50 mL) and washed sequentially with water (50 mL), aqueous saturated sodium bicarbonate solution (50 mL), water (50 mL) and brine (30 mL). The organic layer was dried over magnesium

sulfate, filtered and concentrated *in vacuo*. Purification by flash column chromatography (20% ethyl acetate/hexane) on silica gel gave a complex mixture of products (0.56 g) with identical TLC characteristics as a white foam. The mixture was used without further purification.

A solution of the mixture containing 5-bromo-1,3-dihydro-3-spirocyclohexyl-1-(2'-trimethylsilylethyl)-2,1-benzisothiazoline 2,2-dioxide (0.56 g, 1.25 mmol) and tetrakis(triphenylphosphine)palladium(0) (100 mg) in toluene (25 mL) was stirred under a flow of nitrogen for 25 min. To the solution was added sequentially solutions of 3-chlorophenylboronic acid (0.4 g, 2.5 mmol) in absolute ethanol (5 mL) and potassium carbonate (0.35 g, 2.5 mmol) in water (5 mL). The mixture was heated to 80 °C for 16 h and allowed to cool. The reaction mixture was poured into aqueous saturated sodium bicarbonate solution (50 mL) and the layers were separated. The aqueous phase was extracted with ethyl acetate (3 x 50 mL). The organic layers were combined, washed with water (50 mL) and brine (30 mL) and dried over magnesium sulfate. The solution was filtered, concentrated *in vacuo*, and the residue was purified by flash column chromatography on silica gel (2% ethyl acetate/toluene) and then by HPLC to give the title compound (65 mg) as a low melting yellow foam. HPLC conditions: Zorbax PRO, C18, 10u, 15A, 50 x 250 mm; mobile phase composition and gradient program, 70% water/ 30% AcCN; flow rate, 100 mL/min; injection volume, 120 mg/3 mL MeOH; detection wavelength, 280 nm, 500 PSI; temperature, amb. ^{1}H NMR (DMSO-d_6, 300 MHz), δ 1.47-2.19 (m, 10 H), 6.87 (d, 1 H , J = 8.2 Hz), 7.38 ('d', 1 H, J = 8.1 Hz), 7.46 ('t', 1 H, J = 7.9, 7.7 Hz), 7.56 (dd, 1 H, J = 1.7, 8.2 Hz), 7.62 ('d', 1 H, J = 7.7 Hz), 7.71, ('d', 1 H, J = 1.7 Hz), 7.75 (bs, 1H), 10.55 (bs, 1 H). MS (EI) *m/z* 347 $[M]^+$. Anal. Calcd for $C_{18}H_{18}ClNO_2S$: C, 62.15; H, 5.22; N, 4.03. Found: C, 59.84; H, 5.30; N, 3.57.

Example 2 – Biological Activity

The antiprogestational activity of the compound of Example 1 was demonstrated in a conventional pharmacological test.

Reagents

Growth medium: DMEM (BioWhittaker) containing 10% (v/v) fetal bovine serum (heat inactivated), 0.1 mM MEM non-essential amino acids, 100U/ml penicillin, 100mg/ml streptomycin, and 2 mM GlutaMax (GIBCO, BRL).

Experimental medium: DMEM (BioWhittaker), phenol red-free, containing 10% (v/v) charcoal-stripped fetal bovine serum (heat-inactivated), 0.1 mM MEM non-essential amino acids, 100U/ml penicillin, 100mg/ml streptomycin, and 2 mM GlutaMax (GIBCO, BRL).

Test Procedure

Stock CV-1 cells were maintained in growth medium. Co-transfection was done using $1.2x10^7$ cells, 5 mg pLEM plasmid with hPR-B inserted at Sph1 and BamH1 sites, 10 mg pGL3 plasmid with two PREs upstream of the luciferase sequence, and 50 mg sonicated calf thymus DNA as carrier DNA in 250 ml. Electroporation was carried out at 260 V and 1,000 mF in a Biorad Gene Pulser II. After electroporation, cells were resuspended in growth medium and plated in 96-well plate at 40,000 cells/well in 200 ml. Following overnight incubation, the medium was changed to experimental medium. Cells were then treated with reference or test compounds in experimental medium. Compounds were tested for antiprogestational activity in the presence of 3 nM progesterone. Twenty-four hours after treatment, the medium were discarded, cells were washed three times with D-PBS (GIBCO, BRL). Fifty ml of cell lysis buffer (Promega, Madison, WI) was added to each well and the plates were shaken for 15 min in a Titer Plate Shaker (Lab Line Instrument, Inc.). Luciferase activity was measured using luciferase reagents from Promega.

When evaluated in the above-described test procedure, the compound of Example 1 had an IC_{50} of 900 nM. The IC_{50} is the concentration of test compound that gives half-maximal decrease in 3 nM progesterone induced PRE-luciferase activity.

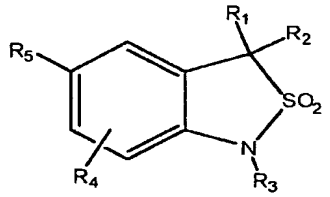
All publications cited in this specification are incorporated herein by reference herein. While the invention has been described with reference to a particularly preferred embodiment, it will be appreciated that modifications can be made without departing from the spirit of the invention. Such modifications are intended to fall within the scope of the appended claims.

What is Claimed:

1. A method of contraception which comprises administering to a female of child bearing age for 28 consecutive days:

a) a first phase of from 14 to 24 daily dosage units of a progestational agent equal in progestational activity to about 35 to about 100 µg levonorgestrel;

b) a second phase of from 1 to 11 daily dosage units, at a daily dosage of from about 2 to 50 mg, of an antiprogestin compound of Formula 1:



1

wherein

R_1, and $R_2$are each, independently, hydrogen, alky, substituted alkyl, hydroxy, alkoxy, substituted alkoxy, aryl, substituted aryl, heteroaryl, substituted heteroary, arylalkyl, heteroarylalkyl, and alkynyl; or

R_1 and R_2 are taken together form a ring and together contain $-CH_2(CH_2)_nCH_2-$, $-CH_2CH_2CMe_2CH_2CH_2-$, $-O(CH_2)_pCH_2-$, $O(CH_2)_qO-$, $-CH_2CH_2OCH_2CH_2-$, $-CH_2CH_2NR_7CH_2CH_2-$; or

R_1 and R_2 are a double bond, said double bond having two methyl groups bonded to the terminal end, having a cycloalkyl group bonded to the terminal end, having an oxygen bonded to the terminal end, or having a cycloether bonded to the terminal end;

R_7 is hydrogen or alkyl of 1-6 carbon atoms;

n = 1-5;

p = 1-4;

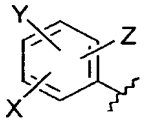
q = 1-4;

R^3 is hydrogen, hydroxyl, NH_2, alkyl, substituted alkyl, alkenyl, alkynyl, substituted or, COR^A;

R^A is hydrogen, alkyl, substituted alkyl, alkoxy, substituted alkoxy, aminoalkyl, or substituted aminoalkyl;

R^4 is hydrogen, halogen, -CN, $-NH_2$, alkyl, substituted alkyl, alkoxy, alkoxy, aminoalkyl, or substituted aminoalkyl;

R^5 is a trisubstituted phenyl ring having the structure,



;

X is halogen, OH, -CN, alkyl, substituted alkyl, alkoxy, substituted alkoxy, thioalkyl, substituted thioalkyl, S(O)alkyl, $S(O)_2$alkyl, aminoalkyl, substituted aminoalkyl, $-NO_2$, perfluoroalkyl, 5 or 6 membered heterocyclic ring containing 1 to 3 heteroatoms, thioalkoxy, $-COR^B$, $-OCOR^B$, or $-NR^CCOR^B$;

R^B is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, alkoxy, substituted alkoxy, aminoalkyl, or substituted aminoalkyl;

R^C is hydrogen, alkyl, or substituted alkyl;

Y and Z are each, independently, hydrogen, halogen, -CN, $-NO_2$, alkoxy, alkyl, or thioalkyl; or

R^5 is a five or six membered heteroaryl ring containing 1, 2, or 3 heteroatoms selected from the group consisting of O, S, SO, SO_2 and NR^6 with said ring carbons being optionally substituted with one or two substituents independently selected from the group consisting of hydrogen, halogen, CN, NO_2 , alkyl, alkoxy, aminoalkyl, COR^D, and NR^ECOR^D;

R^D is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, alkoxy, substituted alkoxy, aminoalkyl, or substituted aminoalkyl;

R^E is hydrogen, alkyl, or substituted alkyl;

R^6 is hydrogen, alkyl, alkoxycarbonyl, or is absent when the nitrogen of NR^6 is bonded to a ring double bond;

or pharmaceutically acceptable salt thereof; and

c) optionally, a third phase of daily dosage units of an orally and pharmaceutically acceptable placebo for the remaining days of the 28 consecutive days in which no antiprogestin, progestin or estrogen is administered; wherein the total daily dosage units of the first, second and third phases equals 28.

2. A method of Claim 1 wherein the progestational agent is levonorgestrel and the anti-progestin compound of Claim 1 wherein:

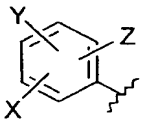
R_1 and R_2 are taken together form a ring and together contain $-CH_2(CH_2)_nCH_2-$;

n = 2-3;

R^3 is hydrogen;

R^4 is hydrogen;

R^5 is a trisubstituted phenyl ring having the structure,



;

X is halogen, OH, -CN, alkyl, alkoxy, thioalkyl, substituted thioalkyl, S(O)alkyl, $S(O)_2$alkyl, aminoalkyl, substituted aminoalkyl, $-NO_2$, perfluoroalkyl, 5 or 6 membered heterocyclic ring containing 1 to 3 heteroatoms, or thioalkoxy;

Y and Z are each, independently, hydrogen, halogen, -CN, $-NO_2$, alkoxy, alkyl, or thioalkyl; or

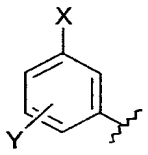
R^5 is a five or six membered heteroaryl ring containing 1, 2, or 3 heteroatoms selected from the group consisting of O, S, and NR^6 with said ring carbons being optionally substituted with one or two substituents independently selected from the group consisting of hydrogen, halogen, CN, NO_2 , alkyl, or alkoxy;

R^6 is hydrogen, alkyl, alkoxycarbonyl, or is absent when the nitrogen of NR^6 is bonded to a ring double bond;

or pharmaceutically acceptable salt thereof.

3. A method of Claim 1 wherein the progestational agent is levonorgestrel and the anti-progestin compound of Claim 1 wherein:

R^5 is a disubstituted phenyl ring having the structure,



;

X is halogen, -CN, or $-NO_2$;

Y is hydrogen, halogen, -CN, $-NO_2$, alkoxy, alkyl, or thioalkyl; or

R^5 is a five or six membered heteroaryl ring containing a heteroatom selected from the group consisting of O, S, and NR^6 with said ring carbons being optionally substituted with one or two substituents independently selected from the group consisting of hydrogen, alkyl halogen, CN, or NO_2 ;

R^6 is hydrogen, or is absent when the nitrogen of NR^6 is bonded to a ring double bond;

or pharmaceutically acceptable salt thereof.

4. The method of claim 1 in which the antiprogestin compound is 5-(3-chlorophenyl)-spiro[2,1-benzisothiazole-3(1H),1'-cyclohexane] 2,2-dioxide or a pharmaceutically acceptable salt thereof.

5. The method of Claim 1 wherein the progestational agent is selected from the group of levonorgestrel, norgestrel, desogestrel, 3-ketodesogestrel, norethindrone, gestodene, norethindrone acetate, norgestimate, osaterone, cyproterone acetate, trimegestone, dienogest, drospirenone, nomegestrol, or (17-deacetyl)norgestimate.

6. A method of Claim 1 which comprises administering to a female of child bearing age consecutively over a 28 day cycle:

a) a first phase of 21 daily dosage units of a progestational agent equal in progestational activity to about 35 to about 100 μg levonorgestrel;

b) a second phase of 3 daily dosage units of an antiprogestin compound of Claim 1, each daily dosage unit containing an antiprogestin compound at a daily dosage of from about 2 to 50 mg; and

c) optionally, 4 daily dosage units of an orally and pharmaceutically acceptable placebo to be administered on each day of the 28-day cycle following the first phase and second phase.

7. A method of contraception which comprises administering to a female of child bearing age over a period of 28 consecutive days:

a) a first phase of from 18 to 21 daily dosage units of a progestostational agent equal in progestational activity to about 35 to about 150 μg levonorgestrel, and ethinyl estradiol at a daily dose range of from about 10 to about 35 μg; and

b) a second phase of from 1 to 7 daily dosage units of an antiprogestin of Claim 1 at a daily dose of from about 2 to 50 mg; and

c) optionally, an orally and pharmaceutically acceptable placebo for each remaining day of the 28 consecutive days.

8. A method of contraception of Claim 7 which comprises administering to a female of child bearing age over a period of 28 consecutive days:

a) a first phase of 21 daily dosage units of a progestostational agent equal in progestational activity to about 35 to about 100 μg levonorgestrel and ethinyl estradiol at a daily dose range of from about 10 to about 35 μg; and

b) a second phase of 3 daily dosage units of an antiprogestin of Claim 1 at a daily dose of from about 2 to 50 mg; and

c) optionally, a third phase of 4 daily dosage units of an orally and pharmaceutically acceptable placebo.

9. A method of contraception which comprises administering to a female of child bearing age over a period of 28 consecutive days:

a) a first phase of from 18 to 21 daily dosage units containing a progestational agent at a daily dose equal in progestational activity to from about 35 to about 150 μg levonorgestrel and ethinyl estradiol at a daily dose range of from about 10 to about 35 μg

b) a second phase of from 1 to 7 daily dose units, each daily dose unit containing an antiprogestin of Claim 1 at a concentration of from 2 to 50 mg and ethinyl estradiol at a concentration of from about 10 to about 35 μg; and

c) optionally, a third phase of daily dosage units of an orally and pharmaceutically acceptable placebo, the total of the daily dosage units being 28.

10. A method of contraception of Claim 9 which comprises administering to a female of child bearing age over a period of 28 consecutive days:

a) a first phase of 21 daily dosage units, each daily dosage unit containing a progestational agent at a daily dose equal in progestational activity to about 35 to about 100 μg levonorgestrel and ethinyl estradiol at a daily dose range of from about 10 to about 35 μg

b) a second phase of 3 daily dose, each daily dose unit containing an antiprogestin of Claim 1 at a concentration of from 2 to 50 mg; and ethinyl estradiol at a concentration of from about 10 to about 35 μg; and

c) optionally, a third phase of 4 daily dosage units of an orally and pharmaceutically acceptable placebo.

11. A pharmaceutically useful kit adapted for daily oral administration which comprises:

a) a first phase of from 14 to 21 daily dosage units of a progestational agent equal in progestational activity to about 35 to about 150 μg levonorgestrel;

b) a second phase of from 1 to 11 daily dosage units of an antiprogestin compound of Claim 1, each daily dosage unit containing an antiprogestin compound at a daily dosage of from about 2 to 50 mg; and

c) a third phase of daily dosage units of an orally and pharmaceutically acceptable placebo;

wherein the total number of the daily dosage units in the first phase, second phase and third phase equals 28.

12. A pharmaceutically useful kit adapted for daily oral administration of Claim 11 which comprises:

a) a first phase of 21 daily dosage units of a progestational agent equal in progestational activity to about 35 to about 150 μg levonorgestrel;

b) a second phase of 3 daily dosage units of an antiprogestin compound of Claim 1, each daily dosage unit containing an antiprogestin compound at a daily dosage of from about 2 to 50 mg; and

c) a third phase of 4 daily dosage units of an orally and pharmaceutically acceptable placebo.

13. A pharmaceutically useful kit adapted for daily oral administration which comprises:

a) a first phase of from 18 to 21 daily dosage units of a progestostational agent equal in progestational activity to about 35 to about 150 μg levonorgestrel and ethinyl estradiol at a daily dose range of from about 10 to about 35 μg; and

b) a second phase of from 1 to 7 daily dosage units of an antiprogestin of Claim 1 at a daily dose of from about 2 to 50 mg; and

c) a third phase of from 0 to 9 daily dosage units of an orally and pharmaceutically acceptable placebo;

wherein the total number of the daily dosage units in the first phase, second phase and third phase equals 28.

14. A pharmaceutically useful kit adapted for daily oral administration of Claim 13 which comprises:

a) a first phase of 21 daily dosage units of a progestostational agent equal in progestational activity to about 35 to about 150 μg levonorgestrel and ethinyl estradiol at a daily dose range of from about 10 to about 35 μg; and

b) a second phase of three daily dosage units of an antiprogestin of Claim 1 administered at a daily dose of from about 2 to 50 mg; and

c) a third phase of 4 daily dosage units of an orally and pharmaceutically acceptable placebo.

15. A pharmaceutically useful kit adapted for daily oral administration which comprises:

a) a first phase of from 18 to 21 daily dosage units, each daily dosage unit comprising a progestational agent at a daily dose equal in progestational activity to from about 35 to about 150 μg levonorgestrel and ethinyl estradiol at a daily dose range of from about 10 to about 35 μg

b) a second phase of from 1 to 7 daily dose units, each daily dose unit containing an antiprogestin of Claim 1 at a concentration of from 2 to 50 mg; and ethinyl estradiol at a concentration of from about 10 to about 35 μg; and

c) a third phase of from 0 to 9 daily dosage units of an orally and pharmaceutically acceptable placebo;

wherein the total number of the daily dosage units in the first phase, second phase and third phase equals 28.

16. A pharmaceutically useful kit adapted for daily oral administration of Claim 15 which comprises:

a) a first phase of 21 daily dosage units, each containing a progestational agent of this invention at a daily dose equal in progestational activity to about 35 to about 150 μg levonorgestrel and ethinyl estradiol at a daily dose range of from about 10 to about 35 μg

b) a second phase of 3 daily dose units, each daily dose unit containing an antiprogestin of Claim 1 at a concentration of from 2 to 50 mg; and ethinyl estradiol at a concentration of from about 10 to about 35 μg; and

c) a third phase of 4 daily dosage units of an orally and pharmaceutically acceptable placebo.

INTERNATIONAL SEARCH REPORT

Int: :onal Application No
PCT/US 00/11642

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K45/06 A61K31/57 A61P15/18 //(A61K31/57,31:425, 31:565)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, EMBASE, MEDLINE, SCISEARCH, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4 093 730 A (BUTTI ADRIANO ET AL) 6 June 1978 (1978-06-06) claim 1	1-39
A	DE 43 30 234 A (SCHERING AG) 9 March 1995 (1995-03-09) column 1, line 1 - line 30 claims 1-8	1-39
A	WO 96 15794 A (BALANCE PHARMACEUTICALS INC) 30 May 1996 (1996-05-30) page 6, line 15 -page 7, line 23	1-39
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 August 2000	30/08/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Bonzano, C

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int. Ional Application No
PCT/US 00/11642

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 521 166 A (GRUBB GARY S) 28 May 1996 (1996-05-28) claim 1 column 2, line 41 - line 60	1-39
A	US 5 733 902 A (SCHNEIDER MARTIN) 31 March 1998 (1998-03-31) column 1, line 13 - line 19	1-39
A	DE 43 44 463 A (SCHERING AG) 29 June 1995 (1995-06-29) page 2, line 1 - line 16	1-39

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-3,5-16 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed.
Present claims 1,4,6-16 relate to a compounds defined by reference to a desirable characteristic or property, namely the progestational activity. The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds.

In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.
Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the combinations containing the progestationals and the antiprogestinics explicitely mentioned in the claims, with due regard to the general idea underlying the present invention.

Claims searched completely: none.
Claims searched incompletely: 1-16.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int[illegible]ional Application No
PCT/US 00/11642

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Information on patent family members

Int· ional Application No
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